

ERYC - erythromycin capsule, coated pellets

Warner Chilcott (US), LLC

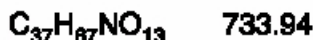
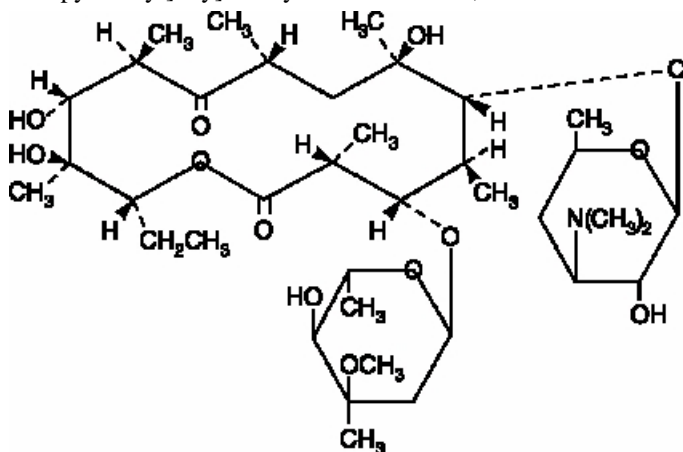
To reduce the development of drug-resistant bacteria and maintain the effectiveness of ERYC[®] and other antibacterial drugs, ERYC should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

ERYC capsules contain enteric-coated pellets of erythromycin base for oral administration. Each ERYC capsule contains 250 mg of erythromycin base. Also contains: lactose NF, povidone USP, FD&C Yellow #6 and other ingredients. The capsule shell contains gelatin NF, titanium dioxide USP, FD&C Yellow #6.

Erythromycin is produced by a strain of *Saccharopolyspora erythraea* (formerly *Streptomyces erythraeus*) and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids but it is the base which is microbiologically active.

Erythromycin base is (3*R**, 4*S**, 5*S**, 6*R**, 7*R**, 9*R**, 11*R**, 12*R**, 13*S**, 14*R**)-4-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl- α -*L*-ribo-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)- β -D-xylo-hexopyranosyl]oxy]-oxacyclotetradecane-2,10-dione.



ERYTHROMYCIN

CLINICAL PHARMACOLOGY

Orally administered erythromycin base and its salts are readily absorbed in the microbiologically active form. Interindividual variations in the absorption of erythromycin are, however, observed, and some patients do not achieve acceptable serum levels. Erythromycin is largely bound to plasma proteins, and the freely dissociating bound fraction after administration of erythromycin base represents 90% of the total erythromycin absorbed. After absorption, erythromycin diffuses readily into most body fluids. In the absence of meningeal inflammation, low concentrations are normally achieved in the spinal fluid, but the passage of the drug across the blood-brain barrier increases in meningitis. The drug is excreted in human milk. The drug crosses the placental barrier, but fetal plasma levels are low. Erythromycin is not removed by peritoneal dialysis or hemodialysis.

In the presence of normal hepatic function erythromycin is concentrated in the liver and is excreted in the bile; the effect of hepatic dysfunction on biliary excretion of erythromycin is not known. After oral administration, less than 5% of the administered dose can be recovered in the active form in the urine.

The enteric coating of pellets in ERYC capsules protects the erythromycin base from inactivation by gastric acidity. Because of their small size and enteric coating, the pellets readily pass intact from the stomach to the small intestine and dissolve efficiently to allow absorption of erythromycin in a uniform manner. After administration of a single dose of a 250 mg ERYC capsule, peak serum levels in the range of 1.13 to 1.68 mcg/mL are attained in approximately 3 hours and decline to 0.30 to 0.42 mcg/mL in 6 hours. Optimal conditions for stability in the presence of gastric secretion and for complete absorption are attained when Erythromycin is taken on an empty stomach.

Microbiology:

Erythromycin acts by inhibition of protein synthesis by binding 50 S ribosomal subunits of susceptible organisms. It does not affect nucleic acid synthesis. Antagonism has been demonstrated *in vitro* between erythromycin and clindamycin, lincomycin, and chloramphenicol.

Many strains of *Haemophilus influenzae* are resistant to erythromycin alone but are susceptible to erythromycin and sulfonamides used concomitantly.

Staphylococci resistant to erythromycin may emerge during a course of therapy.

Erythromycin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Gram-positive Organisms:

Corynebacterium diphtheriae

Corynebacterium minutissimum

Listeria monocytogenes

Staphylococcus aureus (resistant organisms may emerge during treatment)

Streptococcus pneumoniae

Streptococcus pyogenes

Gram-negative Organisms:

Bordetella pertussis

Haemophilus influenzae

Legionella pneumophila

Neisseria gonorrhoeae

Other Microorganisms:

Chlamydia trachomatis

Entamoeba histolytica

Mycoplasma pneumoniae

Treponema pallidum

Ureaplasma urealyticum

Susceptibility Tests:

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure.

Standardized procedures are based on a dilution method¹ (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of erythromycin powder. The MIC values should be interpreted according to the following criteria:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 0.5	Susceptible (S)
1 - 4	Intermediate (I)
≥ 8	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard erythromycin powder should provide the following MIC values:

<u>Microorganism</u>	<u>MIC (µg/mL)</u>
<i>S. aureus</i> ATCC 29213	0.12 - 0.5

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure² requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15 µg erythromycin to test the susceptibility of microorganisms to erythromycin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15 µg erythromycin disk should be interpreted according to the following criteria:

<u>Zone diameter (mm)</u>	<u>Interpretation</u>
≥ 23	Susceptible (S)
14 - 22	Intermediate (I)
≤ 13	Resistant (R)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for erythromycin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 15 µg erythromycin disk should provide the following zone diameters in these laboratory test quality control strains:

<u>Microorganism</u>	<u>Zone Diameter (mm)</u>
<i>S. aureus</i> ATCC 25923	22 - 30

INDICATIONS AND USAGE

Erythromycin is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the diseases listed below:

Upper respiratory tract infections of mild to moderate degree caused by *Streptococcus pyogenes*, *Streptococcus pneumoniae*, or *Haemophilus influenzae* (when used concomitantly with adequate doses of sulfonamides, since many strains of *H. influenzae* are not susceptible to the erythromycin concentrations ordinarily achieved). (See appropriate sulfonamide labeling for prescribing information).

Lower respiratory tract infections of mild to moderate severity caused by *Streptococcus pneumoniae* or *Streptococcus pyogenes*.
Listeriosis caused by *Listeria monocytogenes*.

Pertussis (whooping cough) caused by *Bordetella pertussis*. Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals rendering them noninfectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

Respiratory tract infections due to *Mycoplasma pneumoniae*.

Skin and skin structure infections of mild to moderate severity caused by *Streptococcus pyogenes* or *Staphylococcus aureus* (resistant staphylococci may emerge during treatment).

Diphtheria: Infections due to *Corynebacterium diphtheriae*, as an adjunct to antitoxin, to prevent establishment of carriers and to eradicate the organism in carriers.

Erythrasma: In the treatment of infections due to *Corynebacterium minutissimum*.

Syphilis caused by *Treponema pallidum*: Erythromycin is an alternate choice of treatment for primary syphilis in penicillin-allergic patients. In primary syphilis, spinal fluid examinations should be done before treatment and as part of follow-up after therapy.

Intestinal amebiasis caused by *Entamoeba histolytica* (oral erythromycins only). Extraenteric amebiasis requires treatment with other agents.

Acute pelvic inflammatory disease caused by *Neisseria gonorrhoeae*: Erythromycin lactobionate for injection, USP followed by erythromycin base orally, as an alternative drug in treatment of acute pelvic inflammatory disease caused by *N. gonorrhoeae* in female patients with a history of sensitivity to penicillin. Patients should have a serologic test for syphilis before receiving erythromycin as treatment of gonorrhea and a follow-up serologic test for syphilis after 3 months.

Erythromycins are indicated for the treatment of the following infections caused by *Chlamydia trachomatis*: conjunctivitis of the newborn, pneumonia of infancy, and urogenital infections during pregnancy. When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of uncomplicated urethral, endocervical, or rectal infections in adults due to *Chlamydia trachomatis*.

When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of nongonococcal urethritis caused by *Ureaplasma urealyticum*.

Legionnaires' Disease caused by *Legionella pneumophila*. Although no controlled clinical efficacy studies have been conducted, *in vitro* and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' Disease.

Prophylaxis:

Prevention of Initial Attacks of Rheumatic Fever: Penicillin is considered by the American Heart Association to be the drug of choice in the prevention of initial attacks of rheumatic fever (treatment of *Streptococcus pyogenes* infections of the upper respiratory tract, e.g., tonsillitis or pharyngitis). Erythromycin is indicated for the treatment of penicillin-allergic patients.³ The therapeutic dose should be administered for ten days.

Prevention of Recurrent Attacks of Rheumatic Fever: Penicillin or sulfonamides are considered by the American Heart Association to be the drugs of choice in the prevention of recurrent attacks of rheumatic fever. In patients who are allergic to penicillin and sulfonamides, oral erythromycin is recommended by the American Heart Association in the long-term prophylaxis of streptococcal pharyngitis (for the prevention of recurrent attacks of rheumatic fever).³

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ERYC and other antibacterial drugs, ERYC should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Erythromycin is contraindicated in patients with known hypersensitivity to this antibiotic.

Erythromycin is contraindicated in patients taking terfenadine or astemizole. (See **PRECAUTIONS -Drug Interactions:**).

WARNINGS

There have been reports of prolonged QT syndrome in geriatric patients receiving oral erythromycin products.

There have been reports of hepatic dysfunction, with or without jaundice, occurring in patients receiving oral erythromycin products.

There have been reports suggesting that erythromycin does not reach the fetus in adequate concentration to prevent congenital syphilis. Infants born to women treated during pregnancy with oral erythromycin for early syphilis should be treated with an appropriate penicillin regimen.

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored for creatine kinase (CK) and serum transaminase levels. (See package insert for lovastatin.)

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ERYC Capsules, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS**General:**

Prescribing ERYC in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. Since erythromycin is principally excreted by the liver, caution should be exercised when erythromycin is administered to patients with impaired hepatic function. (See **CLINICAL PHARMACOLOGY** and **WARNINGS**)

CLINICAL PHARMACOLOGY and **WARNINGS**)

There have been reports that erythromycin may aggravate the weakness of patients with myasthenia gravis.

Prolonged or repeated use of erythromycin may result in an overgrowth of nonsusceptible bacteria or fungi. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.

When indicated, incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy.

Information for Patients:

Patients should be counseled that antibacterial drugs including ERYC should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ERYC is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ERYC or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Drug Interactions:

Erythromycin has been reported to significantly alter the metabolism of the nonsedating antihistamines terfenadine and astemizole when taken concomitantly. Rare cases of serious cardiovascular adverse events, including electrocardiographic QT/QTc interval prolongation, cardiac arrest, torsades de pointes, and other ventricular arrhythmias, have been observed. (See CONTRAINDICATIONS). In addition, deaths have been reported rarely with concomitant administration of terfenadine and erythromycin.

There have been postmarketing reports of drug interactions when erythromycin is coadministered with cisapride, resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to the inhibition of hepatic metabolism of cisapride by erythromycin.

There has been an isolated report of drug interaction occurring with the concomitant administration of erythromycin and quinidine in their usual oral forms, resulting in QT prolongation, torsades de pointes and cardiac arrest. Caution and close monitoring is recommended when the drugs are administered concomitantly.

Erythromycin use in patients who are receiving high doses of theophylline may be associated with an increase of serum theophylline levels and potential theophylline toxicity. In case of theophylline toxicity and/or elevated serum theophylline levels, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

Concomitant administration of erythromycin and digoxin has been reported to result in elevated digoxin serum levels.

There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly. Increased anticoagulation effects due to this drug may be more pronounced in the elderly.

Concurrent use of erythromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

Erythromycin has been reported to decrease the clearance of triazolam and midazolam and, thus, may increase the pharmacologic effect of these benzodiazepines.

The use of erythromycin in patients concurrently taking drugs metabolized by the cytochrome P450 system may be associated with elevations in serum levels of these other drugs. There have been reports of interactions of erythromycin with carbamazepine, cyclosporine, hexobarbital, phenytoin, alfentanil, disopyramide, lovastatin, bromocriptine, valproate, terfenadine and astemizole. Serum concentrations of drugs metabolized by the cytochrome P450 system should be monitored closely in patients concurrently receiving erythromycin.

Drug/Laboratory test interactions:

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Long-term (2-year) oral studies conducted in rats with erythromycin base did not provide evidence of tumorigenicity. Mutagenicity studies have not been conducted. There was no apparent effect on male or female fertility in rats fed erythromycin (base) at levels up to 0.25 percent of diet.

Pregnancy:

Teratogenic Effects. Pregnancy Category B:

There was no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed erythromycin base (up to 0.25 percent of diet) prior to and during mating, during gestation, and through weaning of two successive litters. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery:

The effect of erythromycin on labor and delivery is unknown.

Nursing Mothers:

Erythromycin is excreted in human milk. Caution should be exercised when erythromycin is administered to a nursing woman.

Pediatric Use:

See **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION**.

Geriatric Use:

Clinical studies with ERYC did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of the decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

See **WARNINGS** with regard to prolongation of QT syndrome in geriatric patients with erythromycin products.

Elderly patients may experience increased effects of oral anticoagulant therapy while undergoing treatment with erythromycin. (See PRECAUTIONS, Drug Interactions: .)
ERYC 250 mg capsules do not contain sodium.

ADVERSE REACTIONS

The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related. They include nausea, vomiting, abdominal pain, diarrhea and anorexia. Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See WARNINGS). Symptoms of hepatic dysfunction and/or abnormal liver function test results may occur (See WARNINGS).

Rarely, erythromycin has been associated with the production of ventricular arrhythmias, including ventricular tachycardia and torsade de pointes, in individuals with prolonged QTc intervals.

Allergic reactions ranging from urticaria to anaphylaxis have occurred. Skin reactions ranging from mild eruptions to erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely.

OVERDOSAGE

In case of overdosage, erythromycin should be discontinued. Overdosage should be handled with the prompt elimination of unabsorbed drug and all other appropriate measures.

Erythromycin is not removed by peritoneal dialysis or hemodialysis.

DOSAGE AND ADMINISTRATION

Erythromycin is well absorbed and may be given without regard to meals. Optimum blood levels are obtained in a fasting state (administration at least one half hour and preferably two hours before or after a meal); however, blood levels obtained upon administration of enteric-coated erythromycin products in the presence of food are still above minimal inhibitory concentrations (MICs) of most organisms for which erythromycin is indicated.

ADULTS: The usual dose is 250 mg every 6 hours taken one hour before meals. If twice-a-day dosage is desired, the recommended dose is 500 mg every 12 hours. Dosage may be increased up to 4 grams per day, according to the severity of the infection. Twice-a-day dosing is not recommended when doses larger than 1 gram daily are administered.

CHILDREN: Age, weight, and severity of the infection are important factors in determining the proper dosage. The usual dosage is 30 to 50 mg/kg/day in divided doses. For the treatment of more severe infections, this dose may be doubled.

Streptococcal infections: A therapeutic dosage of oral erythromycin should be administered for at least 10 days. For continuous prophylaxis against recurrences of streptococcal infections in persons with a history of rheumatic heart disease, the dose is 250 mg twice a day.

Primary syphilis: 30 to 40 grams given in divided doses over a period of 10 to 15 days.

Intestinal amebiasis: 250 mg four times daily for 10 to 14 days for adults; 30 to 50 mg/kg/day in divided doses for 10 to 14 days for children.

Legionnaires' disease: Although optimal doses have not been established, doses utilized in reported clinical data were those recommended above (1 to 4 grams daily in divided doses).

Urogenital infections during pregnancy due to *Chlamydia trachomatis*: Although the optimal dose and duration of therapy have not been established, the suggested treatment is erythromycin 500 mg, by mouth, 4 times a day on an empty stomach for at least 7 days. For women who cannot tolerate this regimen, a decreased dose of 250 mg, by mouth, 4 times a day should be used for at least 14 days.

For adults with uncomplicated urethral, endocervical, or rectal infections caused by *Chlamydia trachomatis* in whom tetracyclines are contraindicated or not tolerated: 500 mg, by mouth, 4 times a day for at least 7 days.

Pertussis: Although optimum dosage and duration of therapy have not been established, doses of erythromycin utilized in reported clinical studies were 40 to 50 mg/kg/day, given in divided doses for 5 to 14 days.

Nongonococcal urethritis due to *Ureaplasma urealyticum*: When tetracycline is contraindicated or not tolerated: 500 mg of erythromycin, orally, four times daily for at least 7 days.

Acute pelvic inflammatory disease due to *N gonorrhoeae*: 500 mg IV of erythromycin lactobionate for injection, USP every 6 hours for 3 days followed by 250 mg of erythromycin, orally every six hours for 7 days.

HOW SUPPLIED

ERYC[®] (Capsule 696), clear and orange opaque capsules, each containing 250 mg erythromycin as enteric-coated pellets, are available as follows:

N 0430-0696-24 Bottles of 100.

STORAGE CONDITIONS:

Store at controlled room temperature 15° C to 30° C (59° F to 86° F).

REFERENCES

1. **National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically* — Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December 1993.**
2. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests* — Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993.
3. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, The American Heart Association: *Prevention of Rheumatic Fever. Special Report* *Circulation* 78 (4): 1082-1086, October 1988.

Rx only

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